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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,578	03/09/2001	Patrick Hwu	2026-4341	6841

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 09/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/803,578	HWU ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 6/27/06.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,4,7,8,10,40,41,44-46,52-61,71-76 and 79-93 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,4,7,8,10,40,41,44-46,52-61,71-76 and 79-93 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 09 March 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The response filed 6/27/06 is acknowledged. Claim 55 has been amended. Claims 1, 4, 7, 8, 10, 40, 41, 44-46, 52-61, 71-76, and 79-93 are pending and under consideration in the instant office action.

Unless otherwise indicated, previous objection/rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in the 6/27/06 response would be addressed to the extent that they apply to current rejection.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 8/25/2005 was filed after the mailing date of the first action on merit but before the prosecution closes. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. However, it is noted references to Genebank accession numbers fails to comply with 37 CFR 1.97 because they do not contain publication date. A signed IDS will be provided upon correction.

Specification

The status of the application 08/547263, cited on page 17, line 5 of the specification, will need to be updated as necessary.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 7, 40, 41, 71, 72, 79-83, 92, 93 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Altenschmidt et al* (J Immunol 1997;159:5509-15).

Altenschmidt et al teach a method for preparing tumor reactive lymphocytes and a composition comprising: **a**) a population of T lymphocytes transduced with a recombinant genetic construct encoding a chimeric receptor comprising a single chain Fv that is reactive with a tumor antigen ErbB-2, and the modified T lymphocytes were enriched and co-culture with **b**) HC11 and HC11 R2 target cells which are allogenic to the T lymphocytes (the paragraph bridging columns 1 & 2, page 5510). Accordingly, *Altenschmidt et al* anticipate instant claims.

In the response, the applicant argues the Office provides no evidence to establish that the T lymphocytes of *Altenschmid* have an endogenous T–cell receptor reactive with a cell that is allogeneic to the T lymphocyte.

In response, the recitation "*having an endogenous T cell receptor reactive with a cell that is allogeneic to the T lymphocyte*" describes an intrinsic property of a T lymphocyte. It was well known in the art (e.g. Wikipedia, Ctytotoxic T cell) the development of T lymphocyte is such that hematopoetic stem cells in the bone marrow

migrate into the thymus, where they undergo VDJ rearrangement of their beta-chain TcR DNA to form a developmental form of the TcR protein, known as pre-TcR. If that rearrangement is successful, the cells then rearrange their alpha-chain TcR DNA to create a functional alpha-beta TcR complex. This highly-variable genetic rearrangement product in the TcR genes helps create millions of different T cells with different TcRs, helping the body's immune system respond to virtually any protein of an invader, including allogenic protein in an allogenic cell. Since T cell receptor gene is programmed in the genome of a T lymphocyte and all T cells express the T cell receptor/CD3 complex that is capable to interact with MHC class II molecule on the surfact of an APC which presents foreign antigen such as one on an allogenic cell (e.g. Wikipedia, T helper cell), every T cell has an endogenous T cell receptor that is potentially capable of reactive to an allogenic cell, it is only a matter of which allogenic cell, and which corresponding T cell, which are not limited by the claims. Thus, as long as a T cell is present, this limitation is met. Accordingly, the rejection stands.

Claims 1, 7, 40, 45, 52, 61, 71, 72, 76, 79-83, 87, 91-93 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Beecham et al* (J Immunother 2000; 23:332-43).

Beecham et al teach a method for preparing tumor reactive lymphocytes and a composition comprising **a)**. a population of human T lymphocytes transduced with a recombinant genetic construct encoding a chimeric receptor comprising a single chain Fv that is reactive with a tumor antigen CEA, and the modified T lymphocytes were enriched and activated, and then added to **b)**. tumor cell cultures, which are allogenic to

the T lymphocytes (e.g. paragraph bridging pages 334-335). Accordingly, *Beecham et al* anticipate instant claims.

In the remarks, the applicant argues the Office provides no evidence to establish that the T lymphocytes of *Beecham* have an endogenous T –cell receptor reactive with a cell that is allogeneic to the T lymphocyte.

In response, as explained *supra*, the recitation "*an endogenous T cell receptor reactive with a cell that is allogeneic to the T lymphocyte*" describes an intrinsic property of a T lymphocyte. Since T cell receptor gene is programmed in the genome of a T lymphocyte, every T cell has an endogenous T cell receptor which is capable of reactive to an allogenic cell, it is only a matter of which allogenic cell and corresponding T cell, which are not limited by the claims. Thus, as long as a T cell is present, this recitation is met.

Further, *Beecham et al* report "NON-SPECIFIC KILLING OF MIP-101 CELLS ... OCCURRED IN A DOSE-DEPENDENT MANNER" (column 2, page 337), which might just evidence the act of the endogenous T cell receptor reactive with a cell that is allogeneic to the T lymphocyte.

Accordingly, the rejection stands.

It is noted claim 41 has been inadvertently included in this rejection, and has now been excluded.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 7, 8, 40, 41, 45, 46, 52, 56, 58, 61, 71, 72, 75, 76, 79-83, 86, 87, 90-93 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Beecham et al* (J Immunother 2000; 23:332-43), in view of *Terheyden et al* (J Immunol 2000;164:6633-9) and *Munz et al* (J Immunol 1999;162:25-34).

Beecham et al teach an anti-tumor composition comprising a population of human T lymphocyte transduced with a recombinant genetic construct encoding a chimeric receptor comprising a single chain Fv that is reactive with a tumor antigen CEA (pages 336-7). *Beecham et al* teach the composition was made to address an art-known difficulty where tumor-infiltrating lymphocytes from tumor patients are difficult to obtain and often unresponsive to tumors (page 332), and the chimeric receptor lends the cultivated T cells specificity towards recognizing target tumor cells. *Beecham et al* teach a method comprising activating T lymphocyte and then transducing the

lymphocytes with a chimeric receptor gene reactive to a tumor antigen. *Beecham et al* differ from instant claims in that the T cells are activated in a special medium, rather than co-culture with an antigen-presenting cell (a cell allogenic to the lymphocyte), as such *Beecham et al* do not teach a composition comprises both the chimeric T cell and allogenic monocytes such as dendritic cells or other antigen-presenting cells.

Terheyden et al supplemented the deficiency by establishing that it was well known in the art that co-culturing monocytic antigen-presenting cells with T lymphocytes is a routine means of activating T lymphocytes, and has been widely used for T cell expansion, activation, or as a tool for functional investigation. *Terheyden et al* teach dendritic cells directing Th cell differentiation and expansion of tumor-reactive cytotoxic T lymphocytes. Co-culture of dendritic cells with T lymphocytes is a good model system to study cellular interaction during T cell priming and expansion (page 6633-4). *Terheyden et al* differ from instant claims in that they used autologous but not allogenic DCs.

Munz et al supplemented *Beecham et al* in view of *Terheyden et al* by illustrating that allogenic stimulus is as powerful in obtaining potent CTL cells compared to autologous stimulation. *Munz et al* co-cultured PBL with irradiated allogenic (T2 cells) or syngenic (autologous) monocytes (left column, page 26), and report the CTL obtained from allogenic APC allows the stimulation of high avidity cytotoxic T cell. *Munz et al* also teach the need in the art for the allorestricted T cells because the immune system of a cancer patient often be partially destroyed by chemotherapy or factors produced by tumor cells, and under such circumstance, allogenic APCs may be used

for tumor antigen-specific T cell activation in immunosuppressed patients (e.g. the paragraph bridging pages 32-33), and concluded with respect to allogenic stimulated T lymphocytes, "SUCH T CELLS MIGHT INDEED BE USEFUL FOR TUMOR IMMUNOTHERAPY" (e.g. abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the preparation process as taught by *Beecham et al,* with that of *Terheyden et al* and *Munz et al* by co-culturing allogenic APCs with T cells for activation, in place of the AIMV media, with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the special media-induced activation is not target antigen specific, and the co-culture system was a widely used method in the art for a target antigen-specific T cell activation. Given numerous methods known in the art for T cell activation and expansion, this limitation falls within the bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

1. In the remarks, the applicant argues the Office action did not show that the cited references disclose any particular T lymphocyte that contains both a recombinant chimeric receptor reactive with a tumor but also a second receptor reactive with a cell that is allogeneic to the T lymphocyte.

In response, as an initial matter, the instant claims as written do not require the presence of a second receptor; it only requires the T lymphocyte having an endogenous

T cell receptor reactive with an allogenic cell, which is an innate property of a T lymphocyte.

As to the reactive endogenous TcR, the applicant as a skilled artisan should have known well that T cell activation process is a process of triggering high affinity TCR activity. During an immune response, professional APCs absorb foreign material and undergo antigen processing, travelling from the site of infection or transplantation, for example, to the lymph nodes. Once at the lymph nodes, the APC begins to present antigen peptides that are bound to Class II MHC, allowing $CD4^+$ T cells that express high-affinity TcR's to activate (e.g. Wikipedia, T helper cell initial antigen exposure). The media-induced non-specific activation simulates the natural, specific T cell activation, and also requires the expression of high affinity TcR(s) in order for T cell to proliferate. Thus, responding to a foreign antigen such as an allogenic cell is the basic function of a normal T cell, and the T cell activation process as taught by *Terheyden et al* and *Munz et al* utilized such basic function. The fact the T cells reacted to allogenic APCs evidenced that these T cells contain an endogenous T cell receptor reactive with a cell that is allogeneic to the T lymphocyte.

2. Applicant then argues that since Beecham et al used a powerful method of T cell activation, there is no reason to combine the methods of *Terheyden et al* or and *Munz et al* for T cell activation.

In response, the AMIV media-induced T cell activation is not antigen-specific, and often used in experimental studies for quick expansion of T cells and simplifying experimental analysis. Whereas the methods taught by *Terheyden et al* or *Munz et al*

are antigen specific, and often used in anti-tumor studies. A skilled in the art would know well when to use a proper method for T cell activation. It is advantages for *Beecham et al* to use the AMIV media in investigating the tumor killing effect of T cells generated by the chimeric T cell receptor because it eliminates the killing effects induced by a tumor specific APC, and simplifying the analysis for the chimeric TcR. However, if the goal is for tumor killing, it is highly desirable to prepare a T lymphocyte preparation by activating T lymphocytes with an antigen-specific dendritic cells, so that the produced T lymphocytes would be highly antigen-specific, armed with not one but two means, i.e. having both the TcR induced by the antigen-specific APCs, and the engineered chimeric TcR. Thus, the claimed invention as a whole is *prima facie* obvious.

3. Applicant then argues they are unclear where in the *Terheyden et al, Munz* reference that teaches it was well known in the art that co-culturing monocytic APCs with T cell has been widely used.

In response, the previous Office action has referred to specific pages and even columns where the teachings can be found. In summary, the references practiced the techniques. Moreover, since *Munz et al* compared the technique of activating T cell by allogenic or autologous APCs, and concluded "ALLOREACTIVITY AS A SOURCE OF HIGH AVIDITY PEPTIDE-SPECIFIC HUMAN CTL" (the title), they clearly teach the message.

Applicant then pointed to *Munz et al* stating the frequency of allorestricted CTL occurred at twofold lower frequency than autologous.

In response, immediately after, *Munz et al* went on to teach "HOWEVER, POSITIVE SELECTION INCREASES THEIR FREQUENCY" (the abstract). More importantly, *Munz et al* teach why the allorestricted T cells are desirable and when to use them. "IN CANCER PATIENTS, TUMOR REJECTION BY THE [autologous] IMMUNE SYSTEM IS OFTEN INEFFICIENT BECAUSE OF TOLERANCE TOWARD THE TUMOR TISSUE, LOW IMMUNOGENICITY OF THE TUMOR CELLS OR PARTIAL DESTRUCTION OF THE IMMUNE SYSTEM BY CONVENTIONAL ANTITUMOR CHEMOTHERAPY OR FACTORS PRODUCED BY THE TUMOR CELLS. IN THESES CASES, ADOPTIVE TRANSFER OF ALLORESTRICTED CTL CREATED AGAINST TUMOR-ASSOCIATED PEPTIDES MIGHT PRESENT A POSSIBILITY OF REDUCING OR EVEN ELIMINATING THE TUMOR" (e.g. the paragraph bridging pages 32-33, emphasis added). Accordingly, *Munz et al* teach supplementing autologous APCs with allogenic APCs, and do not teach away from generating allorestricted CTL, and the combined teachings render instant claims unpatentable.

Accordingly, for reasons of record and set forth *supra*, the rejection stands.

Claims 4, 10, 44, 53-55, 57, 59, 60, 73, 74, 84, 85, 88, 89 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Beecham et al* (J Immunother 2000; 23:332-43), in view of *Terheyden et al* (J Immunol 2000;164:6633-9) and *Munz et al* (J Immunol 1999;162:25-34) as applied to Claims 1, 7, 8, 40, 41, 45, 46, 52, 56, 58, 61, 71, 72, 75, 76, 79-83, 86, 87, 90-93 above, and further in view of *Nishimura et al* (US Patent 5,830,755), for reasons of record and supra.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave T. Nguyen** can be reached on 571-272-0731. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **William Phillips**, whose telephone number is (571) 272-0548.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is **(866) 217-9197**. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

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PRIMARY EXAMINER

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QJL
September 14, 2006